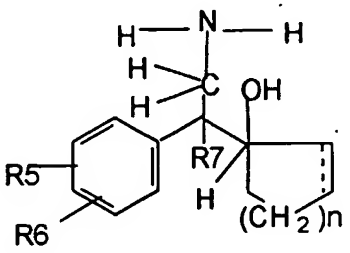
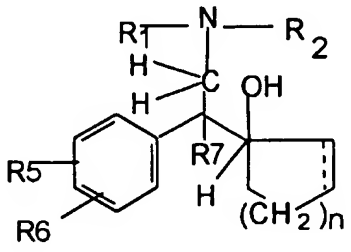
MANUFACTURE OF PHENYL ETHYLAMINE COMPOUNDS, IN PARTICULAR VENLAFAXINE.

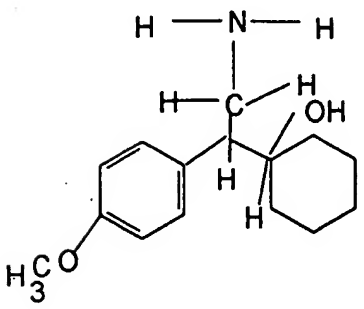
This invention relates to an improved process for the manufacture of hydroxy(cycloalkane or cycloalkene)phenyl ethyl amine compounds of general formula II and its derivatives and in particular the derivative of formula III. More particularly the invention relates to a process for manufacture of precursor of antidepressant of formula V. and its dialkylamino derivative of formula VI.



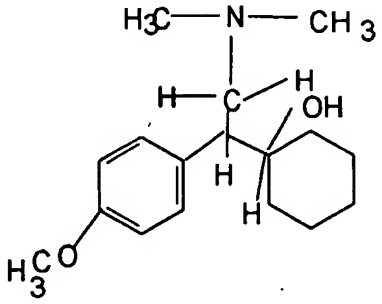
Formula II



Formula III



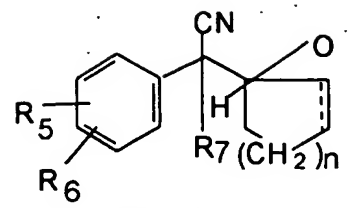
Formula V



Formula VI

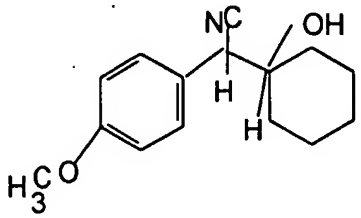
where, either of R5 and R6 independently could be in meta or para position and R5, R6 are independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, alkanamido, halo, trifluoromethyl, or taken together methylenedioxy , n is 0,1,2,3,4; R7 is hydrogen or alkyl of 1-7 carbon atom,.R1 is H or alkyl of 1-3 carbon atom and R2 is alkyl of 1-3 carbon atom ,the dotted line represents optional unsaturation.

The generic version of the antidepressants is represented as formula III and its precursor amine as formula II, and precursor of the amine of formula II is a nitrile of the compound of formula I



Formula I

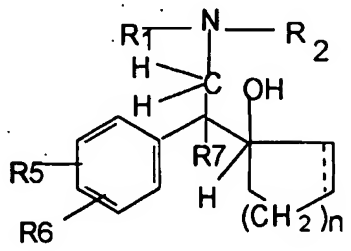
When in formula I either R5 or R6 is in para position and either one of them is -OCH3 and the other is H; R7 is hydrogen; the dotted line representing optional unsaturation is removed ; and n = 2 the compound of formula I is a compound of formula IV which is known as 1-[cyano-(p_methoxyphenyl)methyl]cyclohexanol.



Formula IV

PRIOR ART

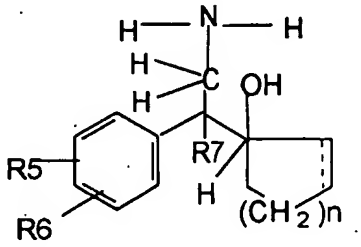
Hydroxy (cyclokene or cycloalkane) (di alkyl) amino phenyl ethyl compound has the generic formula



Formula III

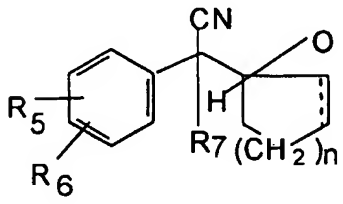
The compound of this general formula has been described in US 4,535,186 and J.Med.Chem33,2809-2905

The said US 4,535,186 and its corresponding EP 0112668A2 teaches the art of manufacture of compound of formula III from its precursor of formula II



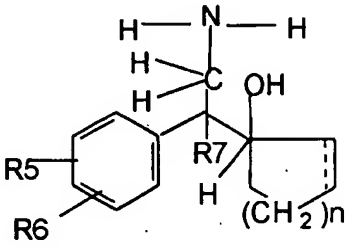
Formula II

The formula II in its turn is arrived at by the reduction of a cyano compound of formula I. The overall process of synthesis of compound of formula III is as under.



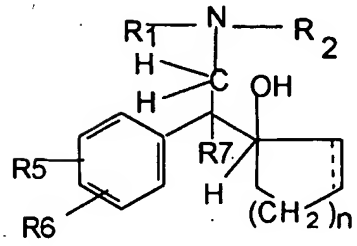
Formula I

Reduction



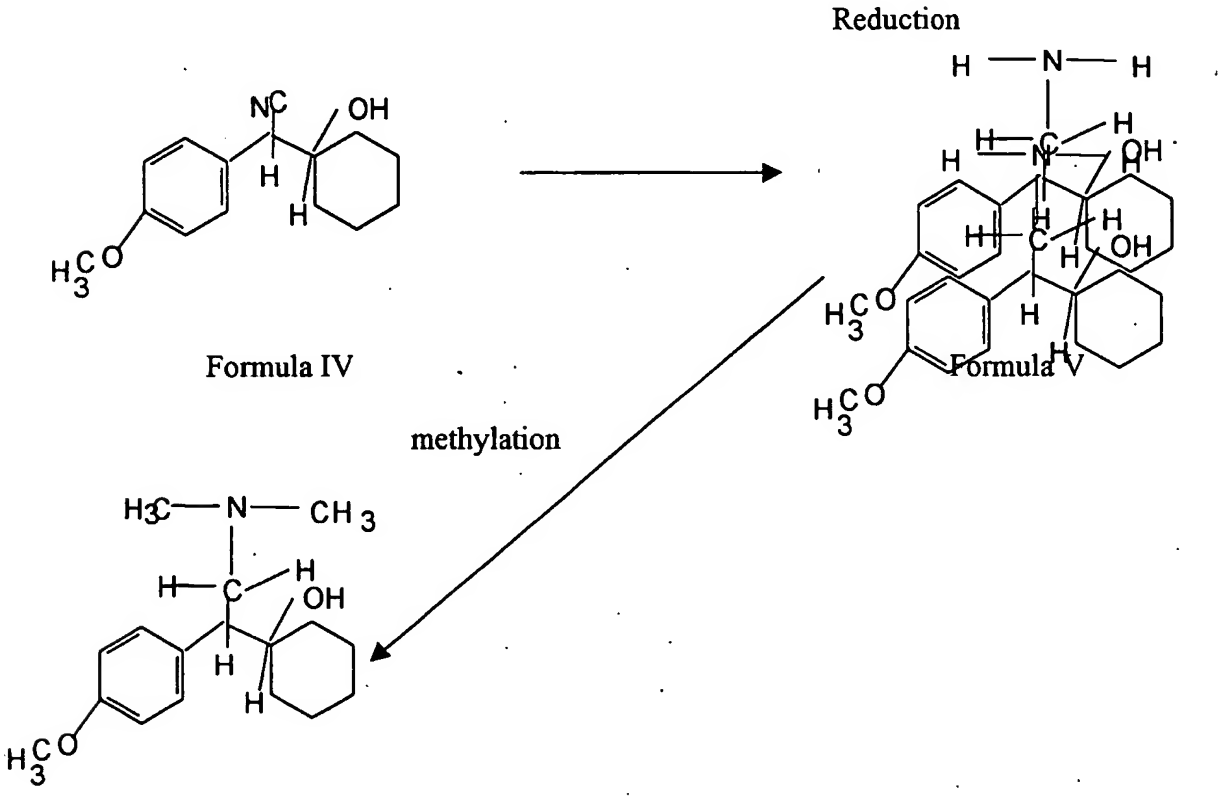
Formula II

Alkylation



Formula III

Reduction of the compound of formula IV gives the compound of formula V, which is chemically known as 1-[2-amino-1-(p-methoxyphenyl)ethyl] cyclohexanol. Methylation of compound of formula V will produce the compound of formula VI which is chemically known as 1-[2-dimethyl (p-methoxyphenyl)ethyl]cyclohexanol or venlafaxine.



Formula IV

Formula V

Formula VI

The reduction process is depicted as above is carried out as follows :

J.Med.Chem 33,2809-2905 ; US 4,535 ,186 and its corresponding EP 0112668A2 teaches the art of reduction of generic version of venlafaxine as well as venlafaxine as under

Catalyst :Raney NickelCorm III

Solvent:Methanol:Methanol ammonia (2:1)

Temp:room temp.

Pressure: 5 Kg/cm2 (72psi)

Time 9hrs

EP 0112669 teaches the various reduction condition as under

Pd/C (10%) and hydrogen in ethanol media

Lithium aluminium hydride in acid media

Rhodium Alumina in ammoniacal ethanol to reduce the nitrile to primary amine

Yet another disclosure WO/0059851 and WO/32556 the said reduction has been carried out using CoCl2 and NaBH4.

According to Chang et al. The precursor cyano methyl compound of the formula IV can be reduced by Na BH4 and BF3 etherate to compound of formula V.

However the above process has one or other disadvantages as depicted as under.

1. Use of expensive organic catalyst like Rh/Al2O3 and BF3 etherate.
2. Use of costly reducing agent like NaBH4.
3. Most of the cases shown above the reducing agent are prone to fire hazard.

The use of Raney Ni, however, reduces the cost of reduction process as the catalyst can be recycled a number of times and hydrogen is a cheaper reducing agent.

Alkylation is performed after the preparation of the primary amine. Methylation of the primary amine is however a well established process for the preparation of dimethyl amine.

In our co-pending application No. 209/MAS/2002 there is disclosed and claimed a method for preparation of compound of formula IV which provides a higher yield compared to those described in the prior art.

The inventors have found that in the process of reduction of compound of formula IV the yield could be improved by the use of a very specific solvent system and a most effective form of catalyst combination out of a particular form of Raney Ni catalyst.

In the present system the required amine of formula V is produced at a better yield than that described in the prior art and at the same time there is provided a system which can be handled in a safer way as the system involves no hazardous chemicals and the reduction at pressure of 120 psi of hydrogen is a safer process at which the inventor carried out successful hydrogenation.

In the present invention the methylation of the amine to dimethyl amine has also been optimized.

OBJECTS

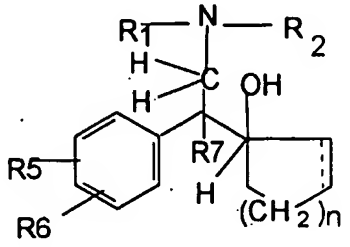
The main objective of the present invention is to produce phenyl ethyl compound of formula II and derivative thereof by an optimised process of reduction through the use of a novel solvent combination which will reduce the cyanocarbinol most effectively.

A further objective of the present invention is to provide a safe method of reduction of the cyano methyl carbinol of fomula IV to amino ethyl carbinol of formula V.

It is yet another objective of the present invention to provide a method for methylating the said amine to the corresponding dimethyl derivative.

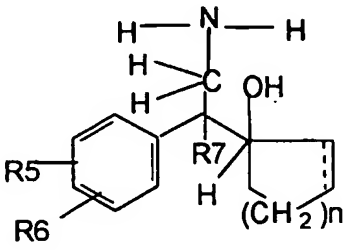
SUMMARY OF INVENTION

A process for the preparation of hydroxy (cycloalkane/cyclokene) phenylethyl amine of the general formula (III)

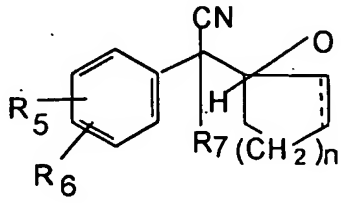


Formula III

comprising alkylation of its precursor amine of general formula (II) which is in turn produced by an effective reduction process from its precursor cyanide having the general formula (I)



Formula II



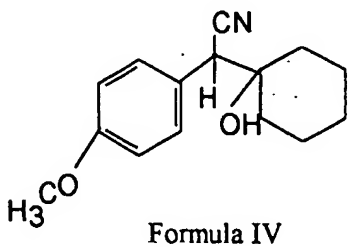
Formula I

where, either of R5 and R6 independently could be in meta or para position and R5, R6 are independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, alkanamido, halo, trifluoromethyl, or taken together methylenedioxy, n is 0,1,2,3,4; R7 is hydrogen or alkyl of 1-7 carbon atom,.R1 is H or alkyl of 1-3 carbon atom and R2 is alkyl of 1-3 carbon atom ,the dotted line represents optional unsaturation.

DETAILED DESCRIPTION OF THE INVENTION

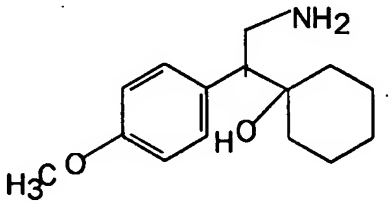
The invention relates to the process for safe manufacture of 1-[2-amino-1-[p-methoxyphenyl)ethyl]cyclohexanol of formula V and methylation of the compound of formula V to the compound 1-[2-dimethyl (p-methoxyphenyl)ethyl]cyclohexanol of formula VI .

In formula I when either R5 or R6 is in para position and either one of them is -OCH3 and the other is H; R7 is hydrogen; the dotted line representing optional unsaturation is removed and n = 2 the compound is a compound of formula IV which is known as 1-[cyano-(p_methoxyphenyl)methyl]cyclohexanol



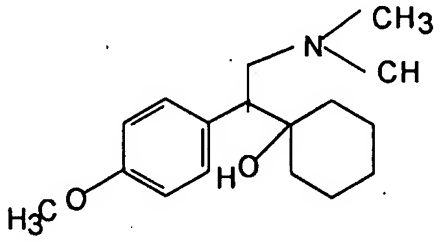
Formula IV

In formula II when either R5 or R6 is in para position and either one of them is –OCH3 and the other is H, R7 is hydrogen; the dotted line representing optional unsaturation is removed and n = 2 the compound is a compound of formula V which is 1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol obtained by the process of reduction of compound of formula IV



Formula V

n formula I when either R5 or R6 is in para position and one of them is –OCH3 and other one is H; R1 and R2 is –CH3; R7 is H ; n=2 and with optional unsaturation removed ,the compound is venlafaxine of formula VI which is obtained by methylation of the compound of formula VI



Formula VI

The reduction is carried out using Raney Ni (CORMIII) as catalyst. The reduction is carried out using a solvent media of aqueous ammonia and methanol. Preferably the combination of aqueous ammonia and methanol is in the ratio of between 1:10 to 1:1.Most preferably the ratio of aqueous ammonia to methanol is 1:5.

The catalyst is used in the proportion of 100 to 20 wt. % of the compound of formula IV. Preferably the catalyst concentration is 75% w/w of the compound of formula IV.

The compound of formula IV has a concentration in the range of 2 to 20 w/v % and preferably in the range of 7 to 13 w/v %. Most preferably the concentration is 6 w/v %.

The catalyst is aged upto 120 days after its preparation and prior to its use. Preferably, the catalyst is aged for a period of between 45 to 30 days after its preparation and before its use. Most preferably, the catalyst is aged for 27 days after its preparation and before its use.

The reduction is carried out at temperature of between –5 to 40°C, preferably at 15 to 30°C and most preferably at 27°C.The pressure is in the range of 30 to 200 psi., preferably 50 to 150 psi. and most preferably 120 psi.

The reduction is carried out for 24 hours, preferably between 8 to 24 hours and most preferably upto 9 hours.

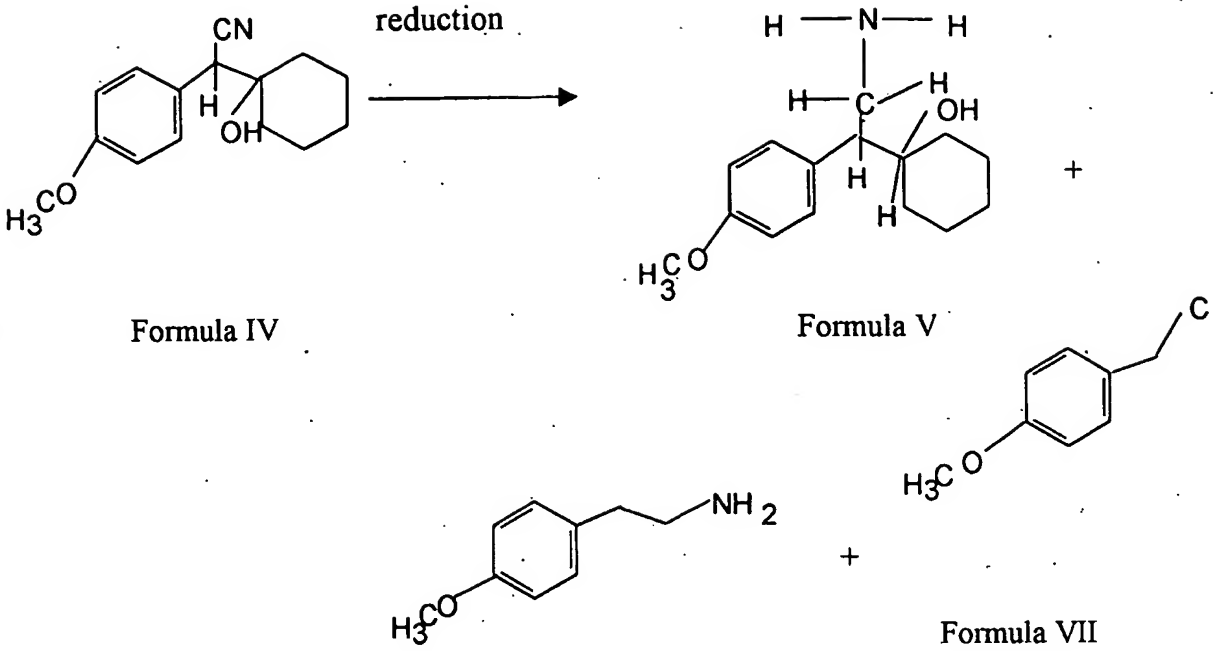
Preferably the methylation is carried using conventional Eshweiler Clarke method.

EXAMPLE

The following process steps are provided to illustrate the invention and are non-limiting examples of the invention

Reduction

Catalytic reduction of compounds of formula IV gives rise to various products which are mixtures of compounds of formula V, VII and VIII. In case of venlafaxine manufacture reduction of compound IV to V various catalyst were tried and results are shown in the table I and II. It is evident from the table as well as following discussion that the reduction process is associated with various by products in different proportion. In this invention effort has been made to increase the yield of the required product V and minimise production of by products .The details discussion illustrates how the reduction as well as methylation step were optimised to get maximum yield and at the same time by products were minimised.



Compound (IV) on subjecting to chemical reduction using catalysts such as LAH, LAH-$AlCl_3$, LAH-H_2SO_4 either lead to compound (VII) by way of its retrogression or there was no reaction at all. Catalytic hydrogenation of compound (IV) using Pd / C at 35 psi and room temperature under neutral as well as acidic conditions gave the starting material back. Similarly, replacing Pd / C by Rh / Al_2O_3 and carrying out the reaction in alcoholic ammonia or acetic acid at 35 psi and room temperature did not give any product. Instead of alcoholic ammonia, when 0.1% NaOH in alcohol was used for the reaction, the reduced retrogression product (VIII) of (IV) was obtained. Finally, hydrogenation of (IV) with 30% w/w of Rh / Al_2O_3 in aq. NH_3-ethanol (1:5) at 35 psi and room temp. could give the required product (V). This compound was used as the reference sample for monitoring hydrogenation reactions using Raney Nickel as the catalyst. Catalytic hydrogenation of compound (IV) over Raney-Ni (50-100% w/w) in alcohol or alcoholic ammonia at 45 to 95 psi and room temperature did not give any product and the starting material was recovered back. Use of 2% alcoholic NaOH or 3-5% of aq. NaOH in alcohol, in place of alcoholic ammonia, resulted in retrogression and subsequent reduction to give compound

(VIII) as the sole product. Finally, with 200% w/w of the Raney Ni catalyst in aq. NH_3-EtOH (1:5) at 35 psi and room temperature, the compound (IV) could be hydrogenated to give the required product (V) in good yield (~90%).

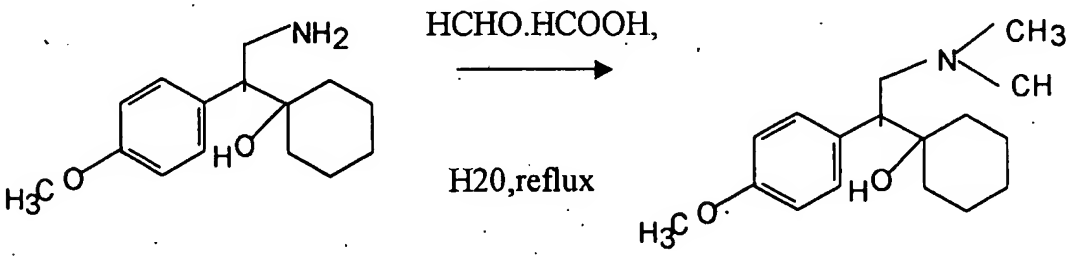
Few more experiments were carried out to see whether lower amounts of the catalyst could be used. In one of such experiment catalyst amount was reduced to 50% w/w, the pressure was increased to 100 psi and the temperature was raised to 50°C. However, it lead to the retrogression followed by reduction and furnished the product(VIII). In another experiment, the catalyst amount taken was 100% w/w, pressure applied was 120 psi and the reaction was carried out at room temp. Interestingly, this reaction gave the required product (V) in good yields. Though, Raney Ni / H_2 system could be used successfully, the reaction always lead to the formation of varying amounts of reduced retrogression product (VIII), without an exception. In order to minimise the formation of compound (VIII) during the reduction of compound (IV), few more parameters were studied in greater detail. The results are summarised below (Table-III).

The pressure of the reaction was fixed at 120 psi, as that was the upper limit of the pressure available for the scale-up studies in India. Three varieties of Raney Ni catalyst were studied such as Raney Ni-type B, Raney Ni-type F and Raney Ni type CORM-III. A reaction with Raney Ni-type B was very slow and did not go to completion even after 24 hrs. The product formed was the mixture of compound (V) and compound (VII), the former being the major and the latter as minor one. Raney Ni-type F caused complete retrogression and gave the reduced product (VIII). A reaction with Raney Ni CORM-III type could go to completion in 8-9 hrs and formed compound (V) as the major product and compound (VIII) as the minor impurity. Encouraged by such an observation, Raney Ni CORM-III type was selected as the catalyst for further studies. Three different catalyst amounts such as 100% w/w, 75% w/w and 50% w/w were studied and it was found that 50% w/w catalyst required 16 hrs for the completion of the reaction, whereas, 75% w/w and 100% w/w catalysts could bring about the reaction to completion in 8-9 hrs. Therefore, 75% w/w amount of the catalyst was taken for further studies. The substrate concentration was studied from 1.6% w/v to 12% w/v and it was found that upto 6% w/v substrate concentration the retrogression is minimum and thereafter the

amount of the retrogression product goes on increasing. The reaction goes smooth at 27°C, the rise in temperature leads to retrogression and at 50°C the reaction gives only the retrogression product (VIII). Raney Nickel catalyst is usually accompanied with a base (NaOH). The traces of base present during hydrogenation, at high pressure, leads to the retrogression. Therefore, the catalyst needs to be washed thoroughly with water before use. Washing the catalyst with 5% acetic acid followed by water did not significantly reduced the concentration of the retrogression product (VIII).

Therefore, washing of the catalyst with excess water was considered to be sufficient to remove the traces of alkali present with the catalyst. The age of the catalyst was also found to play some role in the formation of retrogression product (VIII). The catalyst of the age of three weeks and above gave minimum amount of the retrogression product. Finally, in the optimised conditions, 75% w/w Raney Ni CORM-III catalyst with 3 weeks aging was used after repeated washings with water at 6% w/w substrate conc. In aqueous ammonia-methanol solvent maintained at 27°C under 120 psi Hydrogen pressure for 8-9 hrs. The yield of the product under these conditions was about 90% and contained about 89% of the required product (V) and 11% of the retrogression product (VIII). The impurity, VIII , was removed in the subsequent step.

Step-3 : Methylation



Formula V Formula VI

After the successful reduction of the nitrile function to the amino group, the next task was to carry out the methylation of the amino function. As per the literature, such a conversion can be carried out using Eshwieler Clarke conditions. In the present case we also carried on the same

Eshwieler Clarke reaction for converting compound (V) to compound (VI). In a typical experiment compound (V) was refluxed with formaldehyde, formic acid and water for about 16 hrs. After the work-up the methylated product was directly treated with

IPA.HCl The hydrochloride salt of Venlafaxine was precipitated out whereas, the hydrochloride salt of the reduced retrogression product (VIII) remained in the solution. The final product was well characterized from its spectral data, m.p. and HPLC.

Certain modifications were tried in this step in view of optimizing the yields. In one of the modifications, sodium formate was added to the Eshwieler Clarke reaction mixture. It is supposed to minimize the formylation of amine and thereby increase the yield of the required product. However, in the present case it did not significantly increase the yield of the reaction. In another modification the sequence of addition of formaldehyde and formic acid was reversed. However, this lead to the decrease in yield. In yet another modification, the reaction time was varied from 16 to 18 hrs or 30 hrs. However, in both case there was no increase in the product yield.

Mass Spectra Analysis :

Molecular weight : 249 $[(M+1)^+$ by C.I.M.S.]

Table I : Results of Condensation Reaction for cyano carbinol

Sr. No.	Expt. No.	Mol ratio (2/1)	Base (equiv.)	Catalyst (equiv.)	Solvent	Temp. (^{0}C)	Time (hrs.)	Yield (%)
1	VDG / 00 / 01	1.05	n-BuLi	-	THF	-78	3	82
2	VDG / 00 / 02	1.10	n-BuLi	-	THF	-30	3	72
3	VDG / 00 / 03	1.10	n-BuLi	-	THF	-5	-	-
4	VDG / 00 / 04	1.00	$NaNH_2$	-	THF	-78	3	62
5	VDG / 00 / 05	1.00	$NaNH_2$	-	THF	-5	2	30
6	VDG / 00 / 06	1.00	50% NaOH	TEBAB	H_2O	27	3	Very Poor
7	VDG / 00 / 07	1.00	50% NaOH	Cetrimide	H_2O	27	3	Very Poor
8	VDG / 00 / 08	1.00	50% NaOH	TBAB	H_2O	27	3	Very Poor
9	VDG / 00 / 09	1.10	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	3-4	82
10	VDG / 00 / 10	1.10	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	82
11	VDG / 00 / 11	1.30	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	90
12	VDG / 00 / 12	1.35	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	90
13	VDG / 00 / 13	1.50	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	83
14	VDG / 00 / 14	1.40	10% NaOH (1.0 eq.)	TBAB (0.002 eq.)	H_2O	27	3	92
15	VDG / 00 / 15	1.10	10% NaOH (0.46 eq.)	TBAB (0.001 eq.)	H_2O	27	3	92
16	VDG / 00 / 16	1.40	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	18	6	91
17	VDG / 00 / 17	1.35	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	18	6	91
18	VDG / 00 / 18	1.35	10% NaOH (1.0 eq.)	TBAB (0.002 eq.)	H_2O	15	3	92

Table II : Reduction of Compd. (IV) using different catalysts

Sr. No.	Expt. No.	Catalyst (% w/w)	Solvent	Concn. (% w/v)	P (psi)	Temp. (^{0}C)	Time (hrs.)	Product
1	VDG / 00 / 19	LAH	THF	-	-	RT	15	1
2	VDG / 00 / 20	LAH - $AlCl_3$	Ether	-	-	RT	15	1
3	VDG / 00 / 21	LAH - H_2SO_4	THF	-	-	0	4	Nil
4	VDG / 00 / 22	H_2 / 5% Pd-C (20)	MeOH	-	-	RT	15	Nil
5	VDG / 00 / 23	H_2 / 5% Pd-C (20)	Dioxane	-	35	RT	4	Nil
6	VDG / 00 / 24	H_2 / 10% Pd-C (20)	IPA - AcOH	-	35	RT	4	Nil
7	VDG / 00 / 25	H_2 / 10% Pd-C (20)	IPA . HCl	-	35	RT	4	Nil
8	VDG / 00 / 26	H_2 / 10% Pd-C (35)	AcOH	-	35	RT	4	Nil
9	VDG / 00 / 27	H_2 / Rh - Al_2O_3 (20)	Methanolic NH_3	-	35	RT	4	Nil
10	VDG / 00 / 28	H_2 / Rh - Al_2O_3 (43)	Ethanolic NH_3	-	35	RT	3	Nil
11	VDG / 00 / 29	H_2 / Rh - Al_2O_3 (25)	0.1% NaOH - EtOH	-	35	RT	3	8
12	VDG / 00 / 30	H_2 / Rh - Al_2O_3 (20)	10% NaOH - EtOH	-	35	RT	3	8
13	VDG / 00 / 31	H_2 / Rh - Al_2O_3 (20)	AcOH	-	35	RT	3	Nil
14	VDG / 00 / 32	H_2 / Rh - Al_2O_3 (30)	Aq. NH_3 - MeOH (1 : 5)	-	35	RT	9	4
15	VDG / 00 / 33	H_2 / Rh - Al_2O_3 (100)	Aq. NH_3 - MeOH (1 : 5)	-	35	RT	9	4
16	VDG / 00 / 34	H_2 / Rh - Al_2O_3 (70)	Aq. NH_3 - MeOH (1 : 5)	-	35	RT	9	4

Table II : Reduction of Compd. (IV) using different catalysts

Sr. No.	Expt. No.	Catalyst (% w/w)	Solvent	Concn. (% w/v)	P (psi)	Temp. (^{0}C)	Time (hrs.)	Product
17	VDG / 00 / 35	H_2 / Raney Ni (10)	Methanolic NH_3	-	45	RT	2	Nil
18	VDG / 00 / 36	H_2 / Raney Ni (10)	Methanolic NH_3	-	95	RT	3	Nil
19	VDG / 00 / 37	H_2 / Raney Ni (30)	Methanolic NH_3	-	45	RT	4	Nil
20	VDG / 00 / 38	H_2 / Raney Ni (30)	Methanolic NH_3	-	45	RT	10	Nil
21	VDG / 00 / 39	H_2 / Raney Ni (100)	5% NaOH - MeOH	-	35	RT	1.5	8
22	VDG / 00 / 40	H_2 / Raney Ni (50)	5% NaOH - MeOH	-	35	RT	2.5	8
23	VDG / 00 / 41	H_2 / Raney Ni (50)	3% NaOH - MeOH	-	35	RT	2.5	8
24	VDG / 00 / 42	H_2 / Raney Ni (100)	MeOH	-	35	RT	2.5	Nil
25	VDG / 00 / 43	H_2 / Raney Ni (50)	2% Ethanolic NaOH	-	35	RT	2.5	8
26	VDG / 00 / 44	H_2 / Raney Ni (25)	2% Ethanolic NaOH	-	35	RT	2.5	8
27	VDG / 00 / 45	H_2 / Raney Ni (50)	Ethanolic NH_3	-	120	50	10	8
28	VDG / 00 / 46	H_2 / Raney Ni (50)	Aq. NH_3 - EtOH (1 : 5)	-	100	50	8	8
29	VDG / 00 / 47	H_2 / Raney Ni (200)	Aq. NH_3 - EtOH (1 : 5)	2.0	35	RT	18	4
30	VDG / 00 / 48	H_2 / Raney Ni (100)	Aq. NH_3 - EtOH (1 : 5)	1.6	120	RT	8	4
31	VDG / 00 / 49	H_2 / Raney Ni (50)	Aq. NH_3 - EtOH (1 : 5)	6.0	225	RT	8	4
32	VDG / 00 / 50	H_2 / Raney Ni (25)	Aq. NH_3 - EtOH (1 : 5)	6.0	225	RT	13	4

Table III : Reduction of compound (IV) using Raney Ni (CORM III) in aq. NH_3-alcohol (1:5) at 120 psi

Sr. No.	Expt. No.	Batch size (g.)	Solvent	Conc. (% w/v)	Cat. Amt. (% w/w)	Cat. Age (days)	Temp. (^{0}C)	Time (hrs.)	Crude pdt. (% Yield)	Product V (%)	Impurity VIII (%)
1	VDG / 00 / 51	5	Aq.NH_3-EtOH (1:4)	1.6	100	5	27	8	94	84	16
2	VDG / 00 / 52	21	Aq.NH_3-EtOH (1:4)	7	47.6	33	27	15	74	78	22
3	VDG / 00 / 53	1800	Aq.NH_3-EtOH (1:4)	12	75	39	27	12	-	28	72
4	VDG / 00 / 54	72	Aq.NH_3-MeOH (1:4)	12	75	69	27	10	88	85	15
5	VDG / 00 / 55	72	Aq.NH_3-MeOH (1:4)	12	75	70	27	12	88	86	14
6	VDG / 00 / 56	180	Aq.NH_3-MeOH (1:4)	6	75	110	25	12	84	82	18
7	VDG / 00 / 57	72	Aq.NH_3-MeOH (1:4)	12	75	21	27	11	90	38	62
8	VDG / 00 / 58	180	Aq.NH_3-MeOH (1:4)	6	75	25	27	10	89	89	11
9	VDG / 00 / 59	72	Aq.NH_3-MeOH (1:4)	6	75	28	27	12	91	82	18
10	VDG / 00 / 60	36	Aq.NH_3-MeOH (1:4)	6	75	68	30	10	75	75	25
11	VDG / 00 / 61	36	Aq.NH_3-MeOH (1:4)	6	75	70	30	10	85	80	20
12	VDG / 00 / 62	36	Aq.NH_3-MeOH (1:4)	6	75	75	24	12	-	87	13